REMARKS

I. Initial Comments Regarding the Previously-filed Preliminary Amendment

The Patent Office stated that the Preliminary Amendment filed on December 12, 2003 was not in compliance because the Patent Office states that it failed to indicate the marked changes for the amended specification and claims. The Patent Office requested that applicants provide all pending claims and amended specification with marked changes in the response to the subject Office Action.

Applicants have provided all pending claims, as amended by the Preliminary Amendment, as well as the amended sections of the specification. The claims and specification sections are marked-up to indicate the changes made. Claims 17 and 40 have been withdrawn in the instant amendment, rendering the amendments to these claims moot.

The specification was amended in the Preliminary Amendment to remove a hyperlink and to change the Brief Description of the Figures section to remove the reference to Figure 7. The changes to these sections have been marked.

Finally, the Patent Office stated that applicants erroneously stated that claims 1-42 are pending, although applicants canceled claims 1-13 in the Preliminary Amendment. Applicants have addressed this issue in section II below and regret any confusion this may have caused.

II. Status of the Claims

Claims 1-13 were canceled in the previously-filed Preliminary Amendment.

Following the cancellation of claims 1-13, claims 14-42 were pending in the subject patent application.

Claims 23, 24, 29, 32 and 35-37 have been canceled in the instant amendment.

Claims 14-21 have been withdrawn by applicants in the instant amendment. Claims 40-42 were withdrawn by the Patent Office. Applicants will cancel claims 14-21 and 40-42 when the subject patent application is in condition for allowance.

Claims 22-39 have been examined.

Claim 22 has been amended. Support for the amendments to claim 22 is found throughout the specification as filed, for example on page 4, lines 20-24, on page 19, lines 9-31, in Figure 1 and in claim 32, as filed.

Claim 25 has been amended. Support for the amendment to claim 25 is found in the specification as filed, for example on page 8, lines 6-9.

Claim 25 stands rejected under 35 U.S.C. §101 as directed to non-statutory subject matter.

Claims 22-39 stand rejected under 35 U.S.C. §112, first paragraph, as not enabled.

Claims 22-24, 30, 31, 33 and 34 stand rejected under 35 U.S.C. §102(e) as anticipated by Kovelman et al. (U.S. Patent No. 6,326,480).

Claims 22-39 stand rejected under 35 U.S.C. §103(a) as obvious over Kovelman et al. (US Patent No. 6,326,480), Hagedorn et al. (U.S. Patent No. 5,981,247) and Sherf et al. (U.S. Patent No. 5,670,356).

III. Priority Claim

The Patent Office stated that the subject patent application appears to claim subject matter disclosed in prior application number 10/066,130, filed January 31, 2002, now US Patent Number 6,699,657. The Patent Office further states that a reference to the prior application must be inserted as the first sentence of the specification of this application. Applicants have amended the specification accordingly.

IV. Information Disclosure Statement

The Patent Office stated that it is very inconvenient to review the non-patent literature listed on the IDS filed 3/22/04 during prosecution of Application Number 10/066,130, now US Patent Number 6,699,657. The Patent Office further requested that applicants provide copies of the non-patent literature cited in the IDS filed 3/22/04. For the convenience of the Patent Office, and in order to expedite examination of the instant patent application, applicants provide herewith copies of the non-patent references listed in the IDS filed on 3/22/04.

V. Response to the Rejection of Claim 25 Under 35 U.S.C. §101

The Patent Office rejected claim 25 under 35 U.S.C. §101 as being directed to non-statutory subject matter, namely using a human as a screening tool of the claimed invention. Applicants traverse the rejection and submit the following comments.

Claim 25 was intended to refer to a human *cell*, not to a human. Applicants have corrected this oversight by appropriate amendment of claim 25.

Applicants submit that claim 25 is now compliant with 35 U.S.C. §101 and respectfully request that the rejection of claim 25 under 35 U.S.C. §101 be reconsidered and withdrawn.

VI. Response to the Rejection of Claims 22-39 Under 35 U.S.C. §112, First Paragraph, Enablement

The Patent Office rejected claims 22-39 under 35 U.S.C. §112, first paragraph, as not enabled. The Patent Office states that "the specification, while being enabling for a method to detect a RdRp virus replication by using a compatible cells that comprises a full length cDNA of RdRp virus or at least the cDNA comprising the gene encoding RdRp enzyme, does not reasonable provide enablement for a method to identify a compound or a condition by suing any portion of the genomic sequence of a RdRp virus and by using claimed method without any comparative step for ruling out of the inhibition of the reporter gene is caused by a specific inhibitory effect against the RdRp viral enzymatic activity rather than a non-specific inhibition of reporter gene or host cellular metabolism." *Office Action*, page 4, para. 8. Applicants traverse the rejection and submit the following comments.

Applicants have amended claim 22 to recite that the cell be transfected with cDNA encoding the RdRp (i.e., HCV) enzyme. Support for this amendment to claim 22 is found throughout the specification as filed, for example on page 10, line 33, through page 11, line 8.

Next, the Patent Office states that the specification "does not reasonably provide enablement for a method to identify a compound or a condition by using any portion of the genomic sequence of a RdRp virus and by using claimed method without any comparative step for ruling out if the inhibition of the reporter gene is caused by a specific inhibitory effect against the RdRp viral enzymatic activity rather than a non-specific inhibition of reporter gene or host cellular metabolism." *Office Action*, page 4, para. 8. Applicants traverse the rejection and submit the following.

Applicants have amended claim 22 to recite that any inhibition observed in the presence of a test compound be compared to inhibition observed in the absence of the test compound. Support for this amendment to claim 22 is found throughout the specification as filed, for example in Example 3, pages 26-27. Table 2 of Example 3, appearing on page 27 of the

specification as filed, summarizes Inhibition of Luciferase Activity in the 293B4α Cell Line and demonstrates the comparison of test compounds A-D to vehicle, i.e. the absence of a test compound, which was used as standard. Consequently, all inhibition observed accounts for any in vivo mechanisms and the results represent inhibition due to the presence of the test compounds.

Applicants submit that claim 22 is compliant with the enablement requirement of 35 U.S.C. §112, first paragraph. Claims 23-39 depend directly or indirectly from claim 22. In view of the amendments to claim 22 and the above remarks, applicants respectfully request that the rejection of claims 22-39 under 35 U.S.C. §112, first paragraph, as not enabled, be reconsidered and withdrawn.

VII. Response to the Rejection of Claims 22-24, 30, 31, 33 and 34 Under 35 U.S.C. §102(e)

The Patent Office rejected claims 22-24, 30, 31, 33 and 34 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,326,480 ("the '480 patent"). The Patent Office states that the '480 patent teaches "a method for constructing a plasmid that comprises an antisense-reporter cDNA flanked at both its 5' and 3' ends with 3' and 5' UTR of said RdRp virus' gene also in an antisense orientations respectively." *Office Action*, page 7, para. 17. The Patent Office further states that the '480 patent teaches "a method comprises transfection or transformation of suitable host cells with an antisense reporter gene plasmid as described above and co-culturing said host cells with the RdRp virus, preferably HCV virus isolated from a patient in the presence of a candidate compound and access the virus replication after compared with the predetermined level of the reporter gene expression in the absence of said compound. *Office Action*, page 7, para. 18. The Patent Office continues, stating that the '480 patent "further discloses that within such method, after suitable amount of time co-culturing the virus with said plasmid transfected host cells, the level of reporter gene expression can be evaluated in term of viral replication and evaluating the effectiveness of the tested therapeutic agent or candidate therapeutic agent. *Office Action*, page 7, para. 18. The Patent Office notes that the '480 patent "does not explicitly teach that the viral compatible eukaryotic cells are transfected with full length cDNA of said RdRp virus, the disclosure of culturing said plasmid transformed host cells at the present of said RdRp virus, preferably HCV, indicates that the host cell inherently comprises said virus." *Office Action*, page 8, para. 18. Applicants traverse the rejection and submit the following comments.

Applicants submit that there is a marked distinction between the system described in the '480 patent and the present invention. More particularly, applicants submit that the system of the '480 patent requires that the template employed in the invention must be prepared *in vitro* and subsequently transfected into a host cell. Indeed, Figure 1 of the '480 patent recites the instruction to "transcribe *in vitro*." The system of the '480 patent requires this *in vitro* preparation of the template because it is necessary to remove the poly A tail that accompanies a transcribed sequence. In contrast to the present invention, the teaching of the '480 patent does not have the ability to cleave the poly A tail *in vivo*. Unlike the teaching of the '480 patent, the present invention takes advantage of the δ ribozyme, which operates to remove the poly A tail *in vivo*. Applicants have amended claim 22 to recite the δ ribozyme aspect of the present invention.

Summarily, the template of the '480 system must be made *in vitro* and transfected into a host cell, whereas the template of the present invention is made in the host cell. Additionally, the template of the '480 patent is not recognized as a good template for RNA because, unlike a template of the present invention, it is not created in the cell.

It is well settled that for a cited reference to qualify as prior art under 35 U.S.C. §102, each element of the claimed invention must be disclosed within the reference. "It is axiomatic that for prior art to anticipate under §102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). Applicants submit that the '480 patent teaches a system in which transcription is performed *in vitro*, and the transcript is subsequently transfected. The invention claimed in claim 22, on the other hand, does not require *in vitro* transcription, and as amended recites the δ ribozyme aspect of the invention. Consequently, the '480 patent does not teach each and every element of the claimed invention and, therefore, it cannot anticipate the claimed invention. Accordingly, applicant requests that the rejection of claims 22-24, 30, 31, 33 and 34 under 35 U.S.C. §102(e) be reconsidered and withdrawn.

VIII. Response to the Rejection of Claims 22-39 Under 35 U.S.C. §103(a)

The Patent Office rejected claims 22-39 under 35 U.S.C. § 103(a) as obvious over the '480 patent, US Patent No. 5,981,247 ("the '247 patent") and US Patent No. 5,670,356 ("the 356 patent"). Applicants traverse the rejection and submit the following comments.

Initially, applicants note that it is well known that a *prima facie* case of obviousness requires that in addition to the requirement that the cited document or combination must disclose all aspects of the claimed invention, the combination must contain a suggestion to modify the cited document(s) to arrive at the claimed invention (*see, e.g., Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1988)), and there must be a reasonable expectation of successfully reaching the claimed invention as a result of the modifications (*Boehringer Ingelheim Vedmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)).

Finally, applicants note the Court of Appeals for the Federal Circuit's admonition in *Jones v. Hardy*: "The test under §103 is not whether an improvement or a use set forth in a patent would have been obvious or nonobvious. The test is whether the claimed invention, considered as a whole, would have been obvious or nonobvious." *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984).

Bearing the above in mind, applicants traverse the obviousness rejection. Summarily, applicant submits that when the claimed invention is considered *in toto* and in view of the cited references, alone and/or in combination, the claimed invention is non-obvious and represents a patentable advance in the field.

VIII.A. The Cited Combination Does not Disclose Each and Every Element of the Claimed Invention

The first prong of the *prima facie* case of obviousness requires that the cited combination disclose each and every element of the claimed invention. The combination cited by the Patent Office fails this first prong.

Applicants submit that the '480 patent does not disclose a HCV replication element in antisense orientation. Claim 22 of the present invention has been amended to explicitly include this aspect of the present invention. This element is lacking from the disclosure of the '480 patent.

The '356 patent is of no help in this regard. While applicants agree that the '356 patent discloses the luciferase sequence employed in the present invention, applicants submit that even though the '356 patent discloses a particular sequence of luciferase that is employed in the

present invention, the '356 patent does not disclose a HCV replication element in antisense orientation.

Finally, the '247 patent also fails to disclose a HCV replication element in antisense orientation. As stated above, claim 22 has been amended to explicitly recite this aspect of the claimed invention.

Summarily, the cited combination fails to disclose each and every element of the claimed invention and fails the first prong of the *prima facie* case of obviousness. Consequently, the second and third prongs, the inquiry as to whether suitable motivation to combine the cited references in the manner suggested by the Patent Office is provided, and the inquiry as to likelihood of success are not reached.

Applicants submit that the Patent Office has not presented a *prima facie* case of obviousness. As such, applicants respectfully request that rejection of claims 22-39 under 35 U.S.C. §103(a) be reconsidered withdrawn. Applicants further submit that claims 22-39 are in condition for allowance and respectfully solicits the same.

IX Conclusions

In light of the above amendments and remarks, applicants respectfully submit that the subject patent application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Although it is believed that no additional fee is due in connection with the filing of the instant Response. However, if any fee is due, please charge required fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time is required, such extension is hereby petitioned for, and it is requested that any fee due for such an extension be charged to the above-stated Deposit Account.

Respectfully submitted,

John A. Lamerdin, Ph.D.
Attorney for Applicants
Reg. No. 44,858

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-3575

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